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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,987	TOWNSEND ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/16/04; 2/28/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36,38 and 41-44* is/are pending in the application.

4a) Of the above claim(s) *10,19-36,41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-18, 38, 43, 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

VV

DETAILED ACTION

1. Applicant's election of the four agent species, and mycophenolate mofetil as the fourth agent (see claims 1(d), 3(d), 4(d), 17(d), 18(d) and 44 in the Response to Restriction Requirement, filed 2/28/05 is acknowledged.

Claims 1-36, 38 and 41-44 are pending.

Claims 37 and 39-40 have been canceled previously.

For the record, applicant's previous election with traverse of Group I and the species of agent one is soluble CTLA4, the species of agent two is anti-CD154 antibody and the species of agent 3 is anti-LFA-1 antibody in Paper No. 11 and the species of cardiac allografts in the communication filed 7/22/03 has been acknowledged.

Therefore, claims 1-9, 11-18, 38, 43 and 44 are under consideration as they read on the elected invention and species indicated above in the instant application.

Claims 10, 19-36 and 41-42 are withdrawn from consideration as being drawn to the nonelected invention and species.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 43-44 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the L104EA29YIg (ATCC PTA2104) is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / biological material which produces this molecule. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Although applicant appears to have deposited the L104EA29YIg (ATCC PTA2104) molecule, applicant is invited to clearly set forth whether conditions for deposit of biological materials under 35 USC 112, first paragraph, have been satisfied in the instant application.

Further, it is noted that claim 6 also recites deposited materials, which applicant has indicated have been deposited in compliance with 35 USC 112, first paragraph.

Applicant is required to make clear whether L104EA29YIg (ATCC PTA2104) has been deposited in accordance with the requirements for the deposit of biological materials. If not, claim 6 would be subject to this rejection. Note that claims 43-44 do not recite ATCC numbers.

Alternatively, reciting the entire sequence of the claimed biological material, if disclosed in the application as filed, may satisfy the enablement requirements under 35 USC 112, first paragraph.

4. Applicant's amendment, has obviated the previous rejections under 35 U.S.C. § 112, second paragraph, with respect to the recitations of "regulating", "etanercept" and "anakinra".

5. Claim 1-9, 11-18, 38, 43 and 44 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-9, 11-18 and 38 are indefinite in its recitation of "consisting of administering" and "(d) optionally, at least one pharmaceutical agent selected from the group .... nonsteroidal antiinflammatory drugs, any biological agent targeting antiflammatory cytokine ..... " because the claims appear to be open (i.e. comprising") and closed (i.e. consisting of) at the same time with respect to type and nature of agents that are administered for inhibiting cell-mediated immune responses or treating an immune system disease.

For example, given the recitation of "optionally, at least one pharmaceutical agent" appears to open the claims to the inclusion of a number of pharmaceutical agents, including any "nonsteroidal antiinflammatory drug" or any biological agent targeting antinflammatory cytokine".

B) Claims 43-44 are indefinite in the recitation of "L104EA29YIg1" because its characteristics are not known. The use of "L104EA29YIg" as the sole means of identifying the claimed biological materials renders the claims indefinite because this is merely a laboratory designation which does not clearly define the claimed products, since different laboratories may use the same laboratory designation to define completely distinct biological materials.

Amending the claims to recite the appropriate ATCC Accession Numbers would obviate this rejection.

In addition, the claims are indefinite in that the reference SEQ ID NO: is not recited in the claims. Amending the claims to recite the reference SEQ IDNO: of Figure 6 would obviate this rejection.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

8. Claims 1-7, 9, 12-18 and 38 are rejected under 35 U.S.C. § 102(e) as being anticipated by Digan et al. (US 2002/0142000 A1) (see entire document, including claims, particular claim 28) for the reasons of record.

Applicant's arguments, filed 9/16/04, have been fully considered but are not found convincing for the reasons of record.

Applicant argues that the claims now have been amended to recite "consisting of" rather than "comprising" thereby limiting the claimed methods to use of agent non-inclusive of the immunotoxins described in the Dignan reference.

However, as pointed out above, the instant claims are rejected under 35 U.S.C. § 112, second paragraph, with respect the recitation of "consisting of administering" and "(d) optionally, at least one pharmaceutical agent selected from the group .... nonsteroidal antiinflammatory drugs, any biological agent targeting antiinflammatory cytokine ..... " because the claims appear to be open (i.e. comprising") and closed (i.e. consisting of) at the same time with respect to type and nature of agents that are administered for inhibiting cell-mediated immune responses or treating an immune system disease.

For example, given the recitation of "optionally, at least one pharmaceutical agent" appears to open the claims to the inclusion of a number of pharmaceutical agents, including any "nonsteroidal anitinflammatory drug" or any biological agent targeting an inflammatory cytokine", including the immunotoxins taught by Digan et al. under the broadest reasonable interpretation of the claims.

Digan et al. teach the use of anti-CD3 immunotoxins in combination with other pharmaceutical agents effective in treating various T cell mediated disorders, including acute or chronic transplant rejection, including CTLA4-Ig, anti-LFA-1 antibodies and anti-CD40 ligand antibodies (see Therapeutic Uses of Recombinant Anti-CD3 Immunotoxins on pages 12-16, including paragraph 0198 on pages 12-13). Here, Digan et al. teach various modes of administration, including separate overlapping and systemic administration. Although Digan et al. does not disclose the specific deposited materials comprising CTLA4Ig recited in claim 6, the referenced CTLA4Ig would have had the inherent properties of the CTLA4Ig produced by the deposited materials recited in claim 6.

Furthermore, Digan et al. does teach combination therapy with the newly elected species mycophenolate mofetil (see paragraph [0198] on page 12, column 2).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to inhibit graft rejection in transplant patients with a combination of anti-CD3 immunotoxins in combination including CTLA4-Ig, anti-LFA-1 antibodies, anti-CD40 ligand antibodies and mycophenolate mofetil

It is noted that the claimed methods recite "d. optionally at least one pharmaceutical agent ... nonsteroidal anti-inflammatory drugs" appears to leave the claim open for the inclusion of unspecified ingredients even in major amounts.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Applicant's arguments are not found persuasive.

9. Claims 1-9, 12-18 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320) (1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150).

Applicant's arguments, filed 9/16/04, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments concerning amending the claims to recite "consisting of" and the examiner's rebuttal are essentially the same as that addressed above in the rejection under 35 U.S.C. § 103(e).

As pointed out above, it is noted that the claimed methods recite "d. optionally at least one pharmaceutical agent ... nonsteroidal anti-inflammatory drugs" appears to leave the claim open for the inclusion of unspecified ingredients even in major amounts.

In addition, the prior art provides for the claimed combination of the species of agent one which is soluble CTLA4, the species of agent two which is anti-CD154 antibody and the species of agent 3 which is anti-LFA-1 antibody and mycophenolate mofetil.

For example, Strom et al. teach that the effects of mycophenolate mofetil on purine metabolism are rather selective for activated lymphocytes and, as a consequence, mycophenolate mofetil may replace azathioprine in some drug regimens (see page 454, column 1, paragraph 1, Azathioprine).

In addition, Dana et al. teach the use of anti-CD40 ligand antibodies, particularly in combination with inhibitors of CD80/CD86 interactions with CD28/CTLA4, including CTLA4-Ig (e.g. see paragraphs [0033], [0038], [0079] – [0080]) to inhibit transplant rejection as well as in combination therapies with immunosuppressive compounds such as mycophenolate mofetil (see pagragaph [0079] - [0080]).

Kenyon et al. teach the use of anti-CD40 ligand antibodies in combination with inhibitors of CD80/CD86 interactions with CD28/CTLA4, including CTLA4-Ig, LFA1/ICAM antagonists and mycophenolate mofetil (e.g. see paragraph [0051]) to inhibit transplant rejection (see entire document).

Similarly, Kirk et al. teach the use of anti-CD40 ligand antibodies, particularly in combination with inhibitors of CD80/CD86 interactions with CD28/CTLA4, including CTLA4-Ig (e.g. see paragraphs [0033], [0038] to inhibit transplant rejection.

Therefore, the prior art clearly taught combination therapy for the treatment of graft rejection, including the use of CTLA4-Ig, anti-CD40 ligand antibodies, LFA1/ICAM antagonists and mycophenolate mofetil (MMF).

While applicant has acknowledged that the prior art described each of the agents recited in the claimed methods, applicant argues that there is no evidence showing that the references suggest the claimed

invention, particularly the combination of at least three agents previously and now appears to assert the same is true for at least four agents

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the prior art references teach the advantages of combining immunosuppressive agents that target discrete targets to increase the efficacy of immunosuppression and to decrease the toxicity of immunosuppressive regimens. The teachings of the prior art references indicating success in combining immunosuppressive agents to address these known issues and endpoints would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve such well known problems in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

In contrast to applicant's assertions, the following of record is reiterated for applicant's convenience.

Blazar et al. teach methods of inhibiting antigen specific T cell responses, including inhibiting organ graft rejection, including cardiac transplant (see overlapping paragraph on pages 7-8, Tissue and Organ Transplantation on pages 23-24), with first agent which is an inhibitor of costimulatory signal together with a second agent which inhibits the generation of a delivery proliferative signal in the T cell (see entire document, including Detailed Description of the Invention and the Claims). Blazar et al. teach that the with first agent which is an inhibitor of costimulatory signal , including CTLA4 and anti-LFA-1 antibody as the second agent which inhibits the generation of a delivery proliferative signal in the T cell (See Summary of the Invention on pages 2-4; Detailed Description of the Invention, including pages 6-8, including Bone Marrow Transplantation - Inhibition of GVHD on pages 22-23; Tissue and Organ Transplantation on pages 23-24; and Claims). In addition, Blazar et al. teach treating a variety of subjects (page 19, lines 30-32) in a variety of known modes of administration in effects amounts to achieved the desired result (see Compositions on pages 21 and Uses of the Invention on pages 21-24).

Blazar et al. differs from the claimed invention by not disclosing the combination of a third inhibitor of CD40 ligand interactions in methods of inhibiting transplant rejection. It is noted that Blazar et al. does teach targeting gp39 (page 8, line 6), which is the CD40 ligand.

Larsen et al. teach methods of inhibiting immune responses by blocking CD40L/CD40 and CTLA4/CD28/B7 pathways, including inhibiting transplant rejection and cardiac allografts (column 6, paragraphs 4 and 7), including the combination of CTLA4 and anti-CD40 ligand antibody (e.g. MR1) (see Detailed Description of the Invention (e.g. see columns 5-10 and Examples on columns 10-18) (see entire document). Larsen et al. teach the advantages of inhibiting or blocking both CTLA4/B7 and CD40L/CD40 pathways in promoting prolonged immunosuppression (see column 10, paragraph 3 and Discussion on columns 18-19). Larsen et al. teach treating in a variety of subjects (column 8, paragraph 6) in a variety of known modes of administration depending on the location of the tissue or disease being treated as well as the severity and course of the medical disorder in the judgment of the treating physician (see columns 9-10).

In addition to the teachings of Blazar et al. and Larsen et al., it was known at the time the invention was made that the use of immunosuppressive therapy relies upon a number of basic principles as set forth in Strom et al. These principles include that different agents are used, each of which is directed at a different molecular target and aimed at interrupting several discrete stages in the immune activation pathway (e.g. see page 451 and Figure 36.1). Also, additive-synergistic effects are achieved through the application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agents while increasing the total immunosuppressive effect (see page 451, column 1, paragraph 2).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Larsen et al. to those of Blazar et al. to obtain a combining CTLA4Ig and anti-CD40 ligand antibodies, given their increased immunosuppressive properties, to the Blazar's second agent anti-LFA-1 antibodies which inhibits the generation of a delivery proliferative signal in the T cell to increase the efficacy of immunosuppression in therapeutic regimens to promote the long term survival of transplants, including cardiac allografts at the time the invention was made. According to Blazar et al., Larsen et al. and Strom et al., a person of ordinary skill in the art would have been motivated to combine immunosuppressives to produce an increased immunosuppressive regimen in promoting graft survival at the time the invention was made. In addition to the evidence and expectation of success in combining immunosuppressive agents, including those claimed, the use of combination therapy with biologicals would have had the expected advantage of reducing the toxicity of immunosuppressive regimens associated with transplantation at the time the invention was made, as taught by Strom et al.

A person of ordinary skill in the art would have recognized that the combination of three immunosuppressive agents such as CTLA4Ig, anti-CD40 ligand antibodies and anti-LFA-1 antibodies discussed by the references above would have had advantages of increased immunosuppression and decreased toxicity in achieving antigen-specific nonresponsiveness in promoting long terms survival of transplanted tissues and organs at the time the invention was made. Given the referenced and art known modes of administration at the time the invention was made, the ordinary artisan would have administered the agents locally or systemically as well as sequentially or concurrently given the nature of the grafted tissue or organ and the needs of the patient. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Larsen et al. to those of Blazar et al. to obtain a combining CTLA4Ig and anti-CD40 ligand antibodies, given their increased immunosuppressive properties, to the Blazar's second agent anti-LFA-1 antibodies which inhibits the generation of a delivery proliferative signal in the T cell to increase the efficacy of immunosuppression in therapeutic regimens to promote the long term survival of transplants, including cardiac allografts at the time the invention was made. According to Blazar et al., Larsen et al. and Strom et al., a person of ordinary skill in the art would have been motivated to combine immunosuppressives to produce an increased immunosuppressive regimen in promoting graft survival at the time the invention was made. In addition to the evidence and expectation of success in combining immunosuppressive agents, including those claimed, the use of combination therapy with biologicals would have had the expected advantage of reducing the toxicity of immunosuppressive regimens associated with transplantation at the time the invention was made, as taught by Strom et al.

Given the teachings of newly added Kenyon et al. and Kirk et al., the prior art clearly taught combination therapy for the treatment of graft rejection, including the use of CTLA4-Ig, anti-CD40 ligand antibodies, LFA1/ICAM antagonists and mycophenolate mofetil (MMF).

As indicated previously, the prior art clearly taught specific combinations of anti-CD40L antibodies with either antagonists of LFA-1/ICAM or B7/CD28:CTLA4 interactions (e.g. see the teachings of record reiterated above of Larsen et al. and Blazar et al.).

As indicated by the newly added references, Kenyon et al. and Kirk et al. also teach combination therapies employing all of the agents of the claimed methods, including the newly elected mycophenolate mofetil (MMF).

Furthermore, Strom et al. teach the advantages of mycophenolate mofetil in combination therapies for immunosuppression, including immunosuppression of transplant rejection (see above).

A person of ordinary skill in the art would have recognized that the combination of three immunosuppressive agents such as CTLA4Ig, anti-CD40 ligand antibodies, anti-LFA-1 antibodies and mycophenolate mofetil discussed by the references above would have had advantages of increased immunosuppression and decreased toxicity in achieving antigen-specific nonresponsiveness in promoting long terms survival of transplanted tissues and organs at the time the invention was made. Given the referenced and art known modes of administration at the time the invention was made, the ordinary artisan would have administered the agents locally or systemically as well as sequentially or concurrently given the nature of the grafted tissue or organ and the needs of the patient. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

10. Claims 6, 8 and 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320)(1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150).
as applied to claims 1-9, 12-18 and 38 above
and further in view of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40L antibodies and anti-LFA-1 antibodies, as acknowledged on pages 15-16 of the instant specification and cited in published references).

Applicant's arguments, filed 9/16/04, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above, particularly with respect to over Blazar et al. (WO 95/34320)(1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456).

Applicant's arguments have not been found persuasive.

11. Claims 1-9, 11-18 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Digan et al. (US 2002/0142000 A1) (see entire document, including claims, particular claim 28) in view of Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) and of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40L antibodies and anti-LFA-1 antibodies, as acknowledged on pages 15-16 of the instant specification and cited in published references) for the reasons of record.

Applicant's arguments, filed 9/16/04, have been fully considered but are not found convincing for the reasons of record.

As pointed out above, Digan et al. does teach combination therapy with the newly elected species mycophenolate mofetil (see paragraph [0198] on page 12, column 2).

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above, including the broadest reasonable interpretation of the claimed methods.

12. Claims 6 and 43-44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320) (1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150) as applied to claims 1-9, 12-18 and 38 above and further in view of Peach et al. (US 2003/0219863).

The teachings of Blazar et al. in view of Larsen et al., Strom et al., Kenyon et al. and Kirk et al. are provide above and differ from the claimed methods by not disclosing the L104EA29YIg CTLA4 molecule.

Peach et al. teach the use of L104EA29YIg in treating immune systemdiseases in order to regulate T cell interactions as well as its use with other immunosuppressives, (see entire document, including paragraphs [0067] – [0069]). Peach et al. also teach that the L104EA29YIg binds with higher avidity than CTLA4 (e.g. see Summary of the Invention and Examples).

One of ordinary skill in the art would have been motivated to substitute the L104EA29YIg for CTLA4Ig in the combination therapy taught by of Blazar et al. in view of Larsen et al., Strom et al., Kenyon et al. and Kirk et al. (see above), given its higher binding avidity taught by Peach et al. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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